PATENT SPECIFICATION

1,135,898

NO DRAWINGS

1,135,898

Inventor: JOHN DAVOLL

Date of Application and filing Complete Specification: 19 July, 1968.

No. 33236/67.

(Patent of Addition to No. 1,104,576 dated 28 Dec., 1966.)

Complete Specification Published: 4 Dec., 1968.

Index at acceptance:—C2 C(1F4C2, 1F4D3, 1F4F1, 1F4F2, 2A3, 2A5, 2A12, 2A14, 2B47B4, 2B47G1, 2B47G4, 2B47G5, 2B47G6, 2S17, LZ32Y, LZ213, LZ250, LZ252, LZ321, LZ350, LZ670); **A2** D(2L, 3A); **A5** B2S; **A5** E(1A4B2, 1A4B3, 1A4B4)

Int. Cl.:—C 07 d 51/48

COMPLETE SPECIFICATION

Novel Quinazoline Compounds

We [illegible] & COMPANY, a corporation organised under the laws of the

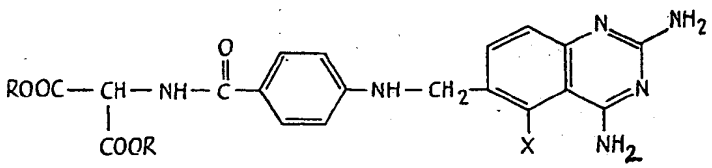
ERRATUM

SPECIFICATION No. 1,135,898
Slip No. 2

Page 1, Heading (Patent of Addition to No. *for* "1104576 dated 28 Dec., 1966)" *read* "1021196 dated 20 Jan., 1965)"

THE PATENT OFFICE
30th June 1969

diamino-6-quinazolinyl)-methyl]amino]benzoyl]amino acid, lower alkyl di-esters, of formula:



(II)

with an acidic or basic hydrolytic agent, under mild conditions; where R is a lower alkyl (i.e., a C_1—C_4 alkyl and preferably methyl or ethyl group, and X has the same meaning specified above.

For the acid hydrolysis a mineral acid such as hydrochloric acid is the preferred hydrolytic agent; for basic hydrolysis, the preferred hydrolytic agent is a suitable alkali metal hydrolytic agent such as an alkali metal hydroxide or carbonate. Sodium

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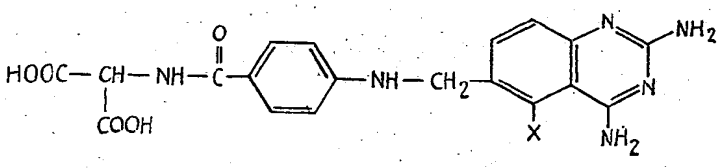
COMPLETE SPECIFICATION

Novel Quinazoline Compounds

We, PARKE, DAVIS & COMPANY, a corporation organised under the laws of the State of Michigan, one of the United States of America, of Joseph Campau at the River, City of Detroit, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

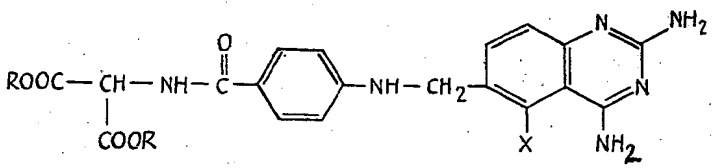
This invention relates to novel chemical compounds and to means of producing the same. More particularly this invention relates to novel dibasic acid compounds derivable from malonic acid and the corresponding di-salts with bases of the acid compounds, which compounds in acid form have the formula:



(I)

where X is a hydrogen atom or chlorine atom or a methyl group.

The compounds of formula I can be produced by reacting an N-{*p*-{[(2,4-diamino-6-quinazolinyl)-methyl]amino}benzoyl}amino acid, lower alkyl di-ester, of formula:



(II)

with an acidic or basic hydrolytic agent, under mild conditions; where R is a lower alkyl (i.e., a C_1—C_4 alkyl and preferably methyl or ethyl group, and X has the same meaning specified above.

For the acid hydrolysis a mineral acid such as hydrochloric acid is the preferred hydrolytic agent; for basic hydrolysis, the preferred hydrolytic agent is a suitable alkali metal hydrolytic agent such as an alkali metal hydroxide or carbonate, Sodium

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hydroxide is preferred for hydrolysis. As will be understood, the product obtained by acid hydrolysis is the free di-acid whereas the product of basic hydrolysis is the di-salt. The latter product can be isolated as the di-acid after treatment with acid and, conversely, the acid product can be isolated as the di-salt after neutralization with the appr priate base. A variety of organic and inorganic bases can be used such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, ammonia, 2-hydroxyethylamine and choline. In obtaining the di-salt, it is preferred for optimum yields to use only the amount (or a slight excess) of base required for formation of the di-salt. Larger amounts may cause decreased yields of the desired product. As a solvent for the hydrolysis, one may employ any of various aqueous, water-miscible non-reactive organic solvents. These include lower alkanols such as methanol, ethanol and isopropanol; ethers such as dioxane, tetrahydrofuran, and diethylene glycol dimethyl ether; glycols such as ethylene and diethylene glycol; and mixtures of these solvents; hydrolysis is conveniently carried out at or below room temperature; at higher temperature yields are less satisfactory. At room temperature (20—25° C.) the reaction is essentially complete within 24 hours.

The compounds of the invention possess pharmacological properties such as antimetabolic (anti-folic acid, anti-thiamine) activity and erythrocyte agglutination suppression (EAS) activity. These properties are demonstrable by standard tests. In the inhibition test (cf. D. W. Woolley, *A Study of Antimetabolites*, John Wiley & Sons, New York, 1952, pp. 66—68), for example, anti-folic activity can be shown similar to that of the known anti-folic substance aminopterin. Thiamine antagonism can be demonstrated (e.g. typically of the order of one milligamma/ml. for 50% inhibition of growth) by a standard method based on that reported by McGlohon, Peterson and Bird, Canadian Journal of Microbiology, *3*, 569, 1957. The compounds therefore are useful as antimetabolites for those applications in which it is desired to antagonize folic acid activity and thiamine activity and thereby inhibit metabolic growth. The compounds also have bacteriostatic activity and as shown in standard tests in relatively low concentration (for example, 50% inhibition at concentrations of the order of 10 gammas/ml.) provide inhibition of organisms such as *S. faecalis R.*, *L. plantarum*, and *L. casei*. The compounds are therefore also useful as bacteriostatic agents for topical application or in aqueous systems for the inhibition of undesirable effects produced by bacteria. For example, the compounds can be used in dilute solution for the prevention of milk spoilage; they can also be used in solution to minimize decomposition and gas formation in self-contained sanitary disposal or sewage units. The compounds also are useful orally or parenterally for the suppression of the normal immune (hemagglutination) response. For example, the di-sodium salt product of Formula I where X is hydrogen is active in the mouse at 10 mg. per kg. (s.c. at day 0 and day 1) to provide complete suppression of hemagglutination at day 5, when tested according to a standard procedure described by Nathan et al., Proc. Soc. Exp. Biol, Med., *107*, 796, 1961.

We are aware of the Milk and Dairies (Preservatives) Regulations 1962, No. 1531, and it is not our intention that the present invention should be used contrary to law.

The invention is illustrated by the following example.

a) A solution of {*p*-{[(2,4-diamino-6-quinazolinyl)-methyl]amino}benzamido}-malonic acid, diethyl ester, hemihydrate (0.95 g.) in hot ethanol (50 ml.) is cooled to 30° C. and treated with 2*N* sodium hydroxide (2.2 ml.). The resulting solid product, {*p* - {[(2,4 - diamino - 6 - quinazolinyl)methyl]amino}benzamido} - malonic acid, di-sodium salt, tetrahydrate, which separates after standing 18 hours is collected by filtration. The corresponding free acid is obtained by dissolving the salt product in water and treating the solution with 2 molar equivalents of dilute hydrochloric acid. The precipitated free acid is removed by filtration, washed with water and dried. Using an ethanol solution of the free acid product the corresponding potassium, ammonium and ethanolamine di-salts are prepared by treating the solution with 2 molar equivalents of the respective base (potassium hydroxide, ammonia or 2-hydroxyethylamine) in an aqueous solution, and recovering the solid product which separates on standing.

By the same procedure but by replacing the ester starting material with an equivalent amount of the corresponding 5-chloro- or 5-methyl derivatives, the resulting salt and acid products are:

{*p* - {[(2,4 - diamino - 5 - chloro - 6 - quinazolinyl)methyl]amino}benzamido}-malonic acid, di-sodium salt, hydrate,

{p - {[(2,4 - diamino - 5 - methyl - 6 - quinazolinyl)methyl]amino}benzamido}-malonic acid, di-sodium salt, hydrate,

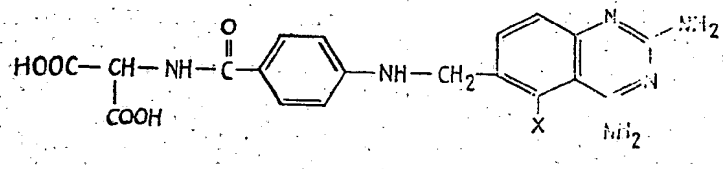
and the corresponding free acids.

b) The dialkyl ester starting material used in paragraph a) can be prepared by the following procedure which procedure is illustrative of a general method which can be employed for the preparation of the dialkyl ester starting materials.

2,4-Diamino-6-quinazoline carbonitrile (7.4 g.) and phenylhydrazine (4.72 ml.) in 50% acetic acid (400 ml.) are hydrogenated at ordinary temperature and pressure, using Raney nickel (J. Org. Chem., 1961, *26*, 1625) until 1152 ml. of hydrogen gas (at 20° C.) have been absorbed. Acetic acid (200 ml.) is added and the mixture heated to 100° C., filtered to remove catalyst and allowed to cool. The crystalline product which separates is collected. This product is 2,4-diamino-6-quinazoline-aldehyde, phenylhydrazone, acetate salt; m.p. 227—230° C. A portion (5.07 g.) of the product and *p*-nitrobenzaldehyde (2.73 g.) are heated at reflux for 2 hours in 50% acetic acid (150 ml.). The mixture is cooled, filtered and the filtrate taken to dryness by evaporation. The residue is treated with cold 2*N* sodium carbonate and the solid product, 2,4 - diamino - 6 - quinazoline - aldehyde, is collected, washed with water and warm ethanol and dried. A portion (0.94 g.) of the product and di-ethyl-(*p*-aminobenzamido)-malonate (J. Am. Chem. Soc., 1949, *71*, 3014; 1.77 g.) in acetic acid (35 ml.) are hydrogenated with Raney nickel until a 1:1 molar ratio of hydrogen gas is absorbed. The solution is filtered, evaporated and the residue treated with 2*N* sodium carbonate solution. The product which separates, {p-{[(2,4-diamino-6-quinazolinyl)methyl]-amino}benzamido}malonic acid, diethyl ester, hemihydrate, is collected; m.p. 194° C. from ethanol. By the same procedure but replacing the quinazoline-carbonitrile with an equivalent amount of the corresponding 5-chloro- or 5-methylquinazolinecarbonitrile, the corresponding 5-chloro- or 5-methylquinazolinylmethylaminobenzamido malonic acid, diethyl ester starting material for the procedure of paragraph a) is obtained.

WHAT WE CLAIM IS:—

1. Di-basic acid compounds of formula:



(I)

and the corresponding di-salts with bases, where X is hydrogen, chlorine or methyl.

2. {p - {[(2,4 - Diamino - 6 - quinazolinyl)methyl]amino}benzamido}malonic acid.

3. {p - {[(2,4 - Diamino - 5 - chloro - 6 - quinazolinyl)methyl]amino}benzamido}malonic acid.

4. {p - {[(2,4 - Diamino - 5 - methyl - 6 - quinazolinyl)methyl]amino}benzamido}malonic acid.

5. The di-sodium salt of {p - {[(2,4 - diamino - 6 - quinazolinyl)methyl]-amino}benzamido}malonic acid.

6. The di-sodium salt of {p - {[(2,4 - diamino - 5 - chloro - 6 - quinazolinyl)-methyl]amino}benzamido}malonic acid.

7. The di-sodium salt of {p - {[(2,4 - diamino - 5 - methyl - 6 - quinazolinyl)-methyl]amino}benzamido}malonic acid.

8. A process for preparing a dibasic acid compound of the formula defined in Claim 1, substantially as described in the foregoing Example.

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